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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/016,737	01/30/1998	GERALD P. MURPHY	8511-007	7366

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/016,737	MURPHY ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-37* is/are pending in the application.

4a) Of the above claim(s) *25 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-24, 26, 28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/15/07 has been entered.

Claims 23, 24, 26, and 28-37 are being examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 23, 31-32, 33-37 remain rejected under 35 USC 103(a) as being obvious over Sallusto et al, 1994 (J Exp Med, 179: 1109-1118, of record), in view of Bigotti G et al, 1991 (Prostate, V19, N1, p.73-87), as evidenced by Inaba K et al, 1987 (Journal of experimental medicine (UNITED STATES), 166 (1) p:182-94, of record), for reasons already of record in paper of 02/15/07.

The response asserts that there is no motivation to combine the ambiguous teaching of Bigotti et al as merely finding Langerhans cell in some low grade prostate tumors with any of the other cited references, which are directed to the maturation of

dendritic cell precursors. The response asserts that it is well known that Langerhans cells are a member of the dendritic cell family, but they are typically found in the epidermis. The response asserts that at the time of the present invention Langerhans cells were thought to contact and process antigen in the epidermis and then migrate to draining lymph nodes where the Langerhans cells would contact naive T cells. The response asserts that the presence of Langerhans cell in a sampling of prostate cancers suggests nothing regarding an antigen that the cells might be presenting, if any. The response asserts that it is just as likely that the Langerhans cells were merely passing through the prostate to a lymph node. The response asserts that there is no comparison with a sample of normal prostate to indicate whether the number of Langerhans cells in elevated from normal tissue. The response asserts that the artisan of ordinary skill has no reason to extend the teachings of Biogotti et al. beyond the use of the presence of Langerhans cells as a prognostic indicator.

The response asserts that Bigotti et al only speculate when teaching that in low grade prostate cancer, Langerhans cells act as antigen-presenting cells, while HLA II molecule may interact primarily or with the aid of Langerhans cells with macrophages and secondarily with T helper lymphocytes causing expansion of cytotoxic T cells, and enhancement of the antibody response to membrane-bound tumor associated antigens, therefore providing a means for controlling the escape of tumor cells from immune surveillance (Bigotti et al, p.85, paragraph under Conclusions). The response asserts that Bigotti et al refer to membrane bound prostate cancer antigens, not soluble antigen as required by the instant claims. The response asserts that Bigotti et al do not refer to antigen specific cytotoxic T cells which typically would result from contact of an antigen

presenting cell with a naive T cell in a peripheral lymph node. The response asserts that further, without additional information relating to, for example, the expression of B7-1 (CD80) and B7-2 (CD86), it is just as likely that the Langerhans cells are involved in a tumor escape mechanism. The response recites Steinbrink et al, 1999, Pisa et al, 1992, and Smith et al, 1994, asserting that it was well known at the time of the invention that many tumors produced and induced the production of immunosuppressive cytokines, such as IL-10. The response asserts that therefore, the presence of Langerhans cells, which can be characterized as immature dendritic cells, would not be likely to successfully uptake and process antigen in the intratumoral environment. The response asserts that in addition, Langerhans cells are considered immature dendritic cells and would not present antigen. The response asserts that it is well known in the art that immature dendritic cells process and only upon maturation present antigen to T cells. The response asserts that further, tetanus toxoid is a bacterial antigen, not a self antigen as is typical for a tumor associated antigen.

The recitation of Steinbrink et al, 1999, Pisa et al, 1992, and Smith et al, 1994 is acknowledged.

The response has been considered but is not found to be persuasive for the following reasons:

The motivation for replacing the model antigen tetanus toxin in the method taught by Sallusto et al, with prostate antigen, taught by Bigotti et al is to make in vitro dendritic cells, that have the ability to present the prostate cancer antigen, using the method taught by Sallusto et al, for potential use in treating prostate cancer, in view that the presence of the dendritic cells, Langershans cells, is correlated with low grade

prostate cancer, and that the presence of Langerhans cells in prostate cancer is a good prognostic indicator, as taught by Bigotti et al.

Moreover, one would have expected that the immature dendritic cells, Langerhans cells, **either in vivo or in vitro**, after being exposed to prostate cancer antigen, would present the prostate antigen, because antigen capature/processing and immunostimulation are the **property of dendritic cells** at different stages of maturation, as taught by Sallusto et al (Sallusto et al, p.1109, first column, second paragraph, bridging second column). Sallusto et al teach that immature dendritic cells, such as Langerhans cells, are scattered throughout the body in non-lymphoid organs. Sallusto et al teach that the **immature** dendritic cells pick up and process antigen, and move to the T-dependent areas of secondary lymphoid organd and that during this **maturation process**, they become mature immunostimulatory DCs that trigger naïve T cells (p.1109, first column, first paragraph).

Concerning immunosuppression by secretion of IL-10 by cancer cells disclosed in the cited references, such immunosuppression does not apply to the **low grade prostate** cancer environment taught by Bigotti et al, because of the following reasons:

1) Steinbrink et al, 1999, submitted by the response, teach a correlation between **advanced** cancers, such as those having metastasis, and the elevated level of IL-10, which elevated level of IL-10 suppresses the immune reponse by T cells, by inducing anergy of T cells (p. 1634, second column, first paragraph). In other words, such anergy of T cells occurs mainly in patients with advanced cancer, such as those having metastatis, which is not low grade prostate cancer, and

2) None of the cited references teach the suppression of T cell response by IL-10 in prostate cancer. Steinbrink et al, however, teach that **depending on the types of tumors**, IL-10 actually has the reverse effect, i.e. **stimulating** immunogenecity and rejection of the tumor (p.1640, second column, third and fourth paragraphs)

Concerning the response assertion that Bigotti et al refer to membrane bound prostate cancer antigens, and not soluble antigen as required by the instant claims, it is noted that it is well known in the art that cancer cells shed their cancer antigens, and thus one would have expected soluble antigens in the vicinity of cancer cells. Further, exposure to soluble antigen to immature dendritic cells in vitro in the presence of GM-CSF and Interleukin-4 to induce their maturation, and their ability to present soluble antigen is taught by Sallusto et al.

Concerning information concerning B7, Applicant argues limitation not in the claims. Further, Sallusto et al teach that the method taught by Sallusto et al produce dendritic cells that maintain the antigen capturing and processing capacity characterisitic of immature dendritic cells in vivo, and having **typical** dendritic morphology, such as expressing high levels of MHC, CD1, FcgammaRII, CD40, **B7**, CD44, and ICAM-1 (Summary). In other words, the Langerhans cells in vivo taught by Bigotti et al would have high level of B7, because it is a property of typical dendritic cells, as taught by Sallusto et al.

2. Claim 24 remains rejected under 35 USC 103(a) as being obvious over Sallusto et al, in view of Bigotti G et al, and as evidenced by Inaba et al, supra, and further in view

of Cohen, PA et al, 1994 (Cancer Research, 54(4): 1055-8) for reasons already of record in paper of 02/15/07.

The response asserts that the combination of Sallusto et al and Bigotti et al does not teach the composition of the claimed invention. The response asserts that the combined references of Sallusto et al, Bigotti et al, Inaba et al and Cohen et al do not provide incentive to combine the references to use a lysate of prostate cancer.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al and Bigotti et al suggests the composition of the claimed invention, supra.

It would have been obvious to use as prostate antigen, a lysate of prostate cancer cells from a prostate cancer patient, because prostate cancer cells would have several prostate cancer-specific antigens, and because a tumor lysate successfully primes the dendritic cells for inducing antigen-specific proliferation of antitumor CD4+ T cells, as taught by Cohen et al, and further because using tumor lysate would be more convenient, and does not require the extra step of purification of the antigen.

3. Claim 26 remain rejected under 35 USC 103(a) as being obvious by Sallusto et al, in view of Bigotti et al, and as evidenced by Inaba et al, supra, as applied to claim 23, and further in view of Lutz et al (of record), for reasons already of record in paper of 02/15/07.

The response asserts that the combination of Sallusto et al, Bigotti et al and/or Inaba et al does not teach the composition of the claimed invention. The response asserts that Luz et al do not prove motivation to make the composition of claim 26.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al, Bigotti et al and Inaba et al suggests the composition of the claimed invention, supra.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the dendritic cells taught by Sallusto et al, Bigotti et al, and Inaba et al, using the immortalizing method taught by Luz et al, because immortalizing dendritic cells would enable maintainance of dendritic cells *in vitro* for long periods of time, as taught by Luz et al.

4. Claims 28-29 remain rejected under 35 USC 103 as being obvious by Sallusto et al, Bigotti et al, Inaba et al, and Cohen et al, supra, as applied to claim 23, and further in view of Taylor et al (of record), for reasons already of record in paper of 02/15/07.

The response asserts that the combination of Sallusto et al, Bigotti et al and/or Inaba et al does not teach the composition of the claimed invention. The response asserts that Taylor et al do not address the teachings of Bigotti et al that the immune response is likely induced in prostate cancer by macrophages. The response asserts that as such the cited references do not teach the composition of claims 28-29.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al, Bigotti et al, and Inaba et al suggests the composition of the claimed invention, supra.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to cryopreserve the dendritic cells taught by Sallusto et al, Bigotti et al, Stites, and Cohen et al, using the cryopreservation method taught by Taylor et al, to preserve the previously isolated dendritic cells for later use.

5. Claim 30 remains is rejected under 35 USC 103 as being obvious by by Sallusto et al, Bigotti et al, and Inaba et al, supra, as applied to claim 23, and further in view of Taylor et al (of record), as applied to claim 28, and Lutz et al, of record, for reasons already of record in paper of 02/15/07.

The response asserts that the combination of Sallusto et al, Bigotti et al, Inaba et al, and Taylor et al does not teach or suggest the composition of the claimed invention. The response asserts that Luz et al do not cure the deficiency of the primary references.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al, Bigotti et al, Inaba et al, and Taylor et al suggests the composition of the claimed invention, supra.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the cryopreserved dendritic cells taught by Sallusto et al, Bigotti et al, Inaba et al and Taylor et al, using the immortalizing method taught by Luz et al, because immortalizing dendritic cells would allow maintainance of dendritic cells *in vitro* for long periods of time, as taught by Luz et al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
September 16, 2007

/Larry R. Helms/

Supervisory Patent Examiner